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The Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure trial (ATMOSPHERE): revised statistical analysis plan and baseline characteristics

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Aims and methods To: (i) describe the baseline characteristics of patients in ATMOSPHERE and the changes in the planned analysis of ATMOSPHERE resulting from the mandated discontinuation of study treatment in patients with diabetes; (ii) compare the baseline characteristics of patients in ATMOSPHERE with those in the Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF); and (iii) compare the characteristics of patients with and without diabetes at baseline in ATMOSPHERE.

Results A total of 7063 patients were randomized into ATMOSPHERE April 2009–April 2014 at 755 sites in 43 countries. Their average age was 63 years and 78% were men. ATMOSPHERE patients were generally similar to those in PARADIGM-HF although fewer had diabetes, renal dysfunction, and were treated with a mineralocorticoid receptor antagonist. In ATMOSPHERE, patients with diabetes differed in numerous ways from those without. Patients with diabetes were older and had worse heart failure status but a similar left ventricular ejection fraction (mean 28%); they had a higher body mass index and more co-morbidity, especially hypertension and coronary heart disease. Mean estimated glomerular filtration rate was slightly lower in those with diabetes compared with those without.

Conclusion ATMOSPHERE will determine whether patients with HF and reduced ejection fraction (particularly those without diabetes) benefit from the addition of a direct renin inhibitor to standard background therapy, including an angiotensin-converting enzyme inhibitor, beta-blocker, and a mineralocorticoid receptor antagonist. ATMOSPHERE will also determine whether aliskiren alone is superior to, or at least non-inferior to, enalapril.

Keywords Heart failure • Aliskiren • Characteristics

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Introduction

The Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure trial (ATMOSPHERE) was designed to make two treatment comparisons, namely (i) the combination of the direct renin inhibitor aliskiren plus enalapril with enalapril alone, and (ii) aliskiren monotherapy with enalapril monotherapy, in a broad spectrum of patients with heart failure and reduced ejection fraction (HF-REF).[1] However, as we have described elsewhere, the premature termination of the Aliskiren Trial In Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE) because of futility and safety concerns, and the subsequent finding in the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) of worse outcomes in the diabetic subgroup treated with aliskiren, led the Clinical Trial Facilitation Group (CTFG) of the Heads of Medicines Agencies in Europe to mandate that all individuals with diabetes in ATMOSPHERE have study drug discontinued, even though both ALTITUDE and ASTRONAUT studied the combination of aliskiren with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and not aliskiren monotherapy (whereas two out of three patients in ATMOSPHERE received either enalapril or aliskiren alone).[2–6] The CTFG also mandated that no further patients with diabetes be enrolled in ATMOSPHERE (and that patients developing diabetes during the trial be switched to conventional therapy). Despite the uncertainty created by the findings in the above trials and the aforementioned regulatory restrictions, ATMOSPHERE completed recruitment in April 2014.

ATMOSPHERE will shortly complete follow-up as the pre-specified number of patients with a primary endpoint has almost accrued, even though events among patients with diabetes occurring after the regulatory intervention described above are not included in this total. In this paper we describe the baseline characteristics of the patients randomized into ATMOSPHERE as well as the various changes in the planned analysis of ATMOSPHERE resulting from the mandated discontinuation of study treatment in patients with diabetes. The baseline characteristics are compared with those of patients in the recently reported Prospective comparison of Angiotensin Receptor neprilysin inhibitors with Angiotensin converting enzyme inhibitors to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) and, in view of the regulatory concerns raised, we also compare the characteristics of patients with and without diabetes at baseline in ATMOSPHERE.[7]

Methods

ATMOSPHERE summary of design and original analysis plan

The ATMOSPHERE study rationale and design has been described in detail elsewhere.[1] Briefly, ATMOSPHERE is a randomized, double-blind, double-dummy, parallel-group, active control, three-arm, long-term morbidity and mortality trial evaluating the efficacy and safety of the combination of aliskiren plus enalapril in comparison with enalapril alone, as well as evaluating aliskiren as monotherapy in comparison with enalapril. Patients were required to be 18 years of age and older, have chronic symptomatic heart failure (New York Heart Association functional class II–IV), left ventricular ejection fraction (LVEF) ≤35% and an elevated plasma BNP or *N*-terminal pro B-type natriuretic peptide (NT proBNP), as summarized in *Table 1*. Patients were randomized 1:1:1 to enalapril, the combination of enalapril plus aliskiren, or aliskiren alone. Eligible patients were required to undergo an active run-in period of between 5 weeks and 12 weeks comprising exposure first to enalapril at either 10 mg/day or 20 mg/day depending on previous ACE inhibitor dosage, up-titrating (if required) to 20 mg/day. Patients then had aliskiren 150 mg/day added to the tolerated dose of enalapril. Patients tolerating both agents were then randomized to enalapril 5 or 10 mg twice daily to continue at highest tolerated dose, the combination of aliskiren and enalapril with aliskiren up-titrated to 300 mg/day or aliskiren 150 mg/day, up-titrated to 300 mg/day.

The original primary objectives of ATMOSPHERE were to test whether the combination of aliskiren and enalapril is superior to enalapril monotherapy in delaying time to the first occurrence of cardiovascular death or hospitalization due to heart failure, and to test whether aliskiren monotherapy is superior, or at least non-inferior, to enalapril monotherapy using the same endpoint. The annual event rate for this composite outcome was estimated to be 14.5% in the control (enalapril monotherapy arm) assuming an estimated annual drop-out rate of 4%. For superiority of the combination of enalapril plus aliskiren over enalapril alone, the study had 82% power to detect a 15% reduction in the primary endpoint; for superiority of aliskiren monotherapy over enalapril monotherapy, the power was 80%. The trial also had >80% power for non-inferiority (aliskiren vs. enalapril), assuming a 6% difference in favour of aliskiren (and a non-inferiority margin of 10.4% calculated using the 95–95 method with preservation of 50% of the benefit of enalapril over placebo)

ATMOSPHERE revised analysis plan

The statistical analysis plan was amended in light of the regulatory intervention to discontinue study drug in patients with diabetes.

The major changes are:

1 In the main efficacy analyses, in patients with diabetes, follow-up for trial end-points will be censored on the date of the local implementation of health authority or ethics committee requests to stop study treatment. Patients with renal impairment in France and Ireland and all patients from Venezuela will also be censored in a similar fashion because of specific study drug discontinuation requests in those countries. Individuals with diabetes but off study drug have been followed up as stipulated in the trial protocol and all events reported during the total duration of follow-up (even if occurring after mandatory discontinuation of study drug) will be included in safety analyses. We believe that this censoring will not introduce bias as stopping of treatment was not determined by either the investigator or sponsor and was not related to a specific study treatment or decided with knowledge of treatment effect (or any other unblinded data) in these patients. Censoring is solely dependent on patient baseline characteristics (country and diabetes/renal function) and applies to patients who had been off treatment before to the health authority or ethics committee requests to stop study treatment
2 Comparison of enalapril plus aliskiren with enalapril monotherapy in patients without diabetes has been added as an additional superiority hypothesis (*Figure 1*). Because of the large size of the

Table 1 Key design features of ATMOSPHERE and PARADIGM-HF

	ATMOSPHERE (*N* = 7063)	PARADIGM-HF (*N* = 8442)
Inclusion criteria		
Age, years	≥18	≥ 18
NYHA class	II–IV	II–IV
LVEF, %	≤35%	≤40% (amended to ≤35%)
Natriuretic peptides	BNP ≥150 pg/mL (NT-proBNP ≥ 600 pg/mL) or BNP ≥ 100 pg/mL (NT-proBNP ≥ 400 pg/mL) if unplanned hospitalization for HF within the last 12 months	BNP ≥150 pg/mL (NT-proBNP ≥600 pg/mL) or BNP ≥100 pg/mL (NT-proBNP ≥400 pg/mL) if unplanned hospitalization for HF within the last 12 months
Background therapy		
ACE inhibitor/ARB	Treatment with an ACE inhibitor at a stable dose (equivalent to at least enalapril 10 mg daily)	Treatment with an ACE inhibitor or an ARB at a stable dose (equivalent to at least enalapril 10 mg daily)
Beta-blocker	Treatment with a beta-blocker (unless not tolerated or contraindicated)	Treatment with a beta-blocker (unless not tolerated or contraindicated)
MRA	Use of both an ARB and a MRA prohibited. Either one could be prescribed but only with extreme caution and very rigorous safety monitoring. Requirement to warn patient about risks of renal dysfunction and hyperkalaemia	Protocol amended to state that a MRA should be considered in all patients, taking account of renal function, serum potassium, and tolerability
Exclusion criteria		
eGFR, ml/min.1.73 m^2	<40 (screening), <35 (run-in/randomization)†	<30 (screening), <30 (run-in/randomization)†
Systolic blood pressure, mmHg	<95 (screening), <90 (run-in/randomization) or symptomatic hypotension	<100 (screening) <95 (run-in/randomization) or symptomatic hypotension
Potassium, mmol/L	≥5.0 (screening), ≥5.2 (run-in/randomization)	>5.2 (screening), >5.4 (run-in/randomization)
Run-in*		
First period	Enalapril 10 mg bid**	Enalapril 10 mg bid
Second period	Enalapril 10 mg bid plus aliskiren 150 mg qd**	LCZ696 200 mg bid
Comparison	Enalapril 10 mg bid** Aliskiren 300 mg/day + enalapril 10 mg bid** Aliskiren 300 mg/day	Enalapril 10 mg bid LCZ696 200 mg bid
Recruitment period	2009–2014	2009–2012‡

ATMOSPHERE, aliskiren trial to minimize outcomes in patients with heart failure trial; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PARADIGM-HF, prospective comparison of angiotensin receptor neprilysin inhibitors with angiotensin converting enzyme inhibitors to determine impact on global mortality and morbidity in heart failure trial.

*Target doses patients must achieve and tolerate.

†Or a decrease of eGFR of more than 25% between screening and randomization visit (amended to 35% in PARADIGM-HF).

‡The last patient entered the run-in in 2012 but was randomized in 2013.

**Up to 1/5 patients could be enrolled in a low-dose stratum (enalapril 5mg bid).

subgroup of patients without diabetes, significant imbalances in baseline characteristics are not expected between the treatment groups. Should such imbalances occur, sensitivity analyses adjusting the treatment effect for the appropriate covariates will be carried out.

3 Of the two original secondary endpoints, only change from baseline to 12 months in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ) has been retained (change in BNP level from baseline to 4 months has been removed as it was felt that this surrogate endpoint was not considered clinically important).[8]

A gate-keeping procedure that combines hierarchical and simultaneous testing based upon Bonferroni inequality will be used to ensure control of the type I error rate for the primary and secondary endpoints.[9] This multiple testing procedure is illustrated in *Figure 1*.

The revised power calculations for superiority are shown in *Table 2*. The power for the primary analyses is largely preserved and the power to show a mean difference of 2 points in the KCCQ secondary endpoint is 94%.

Comparison of ATMOSPHERE and PARADIGM-HF

The present report describes the baseline characteristics of the patients randomized in ATMOSPHERE following the screening and open-label run-in period of the study. These characteristics are compared with the baseline findings at the same time-point in PARADIGM-HF, which also had a sequential, two-treatment, active run-in period.[10,11] PARADIGM-HF was similar, but not identical, in design to ATMOSPHERE, as illustrated in *Table 1* and discussed later.

Comparison of patients with and without diabetes in ATMOSPHERE

A breakdown of patient characteristics according to diabetes status at baseline is also reported, in view of the specific concerns raised in

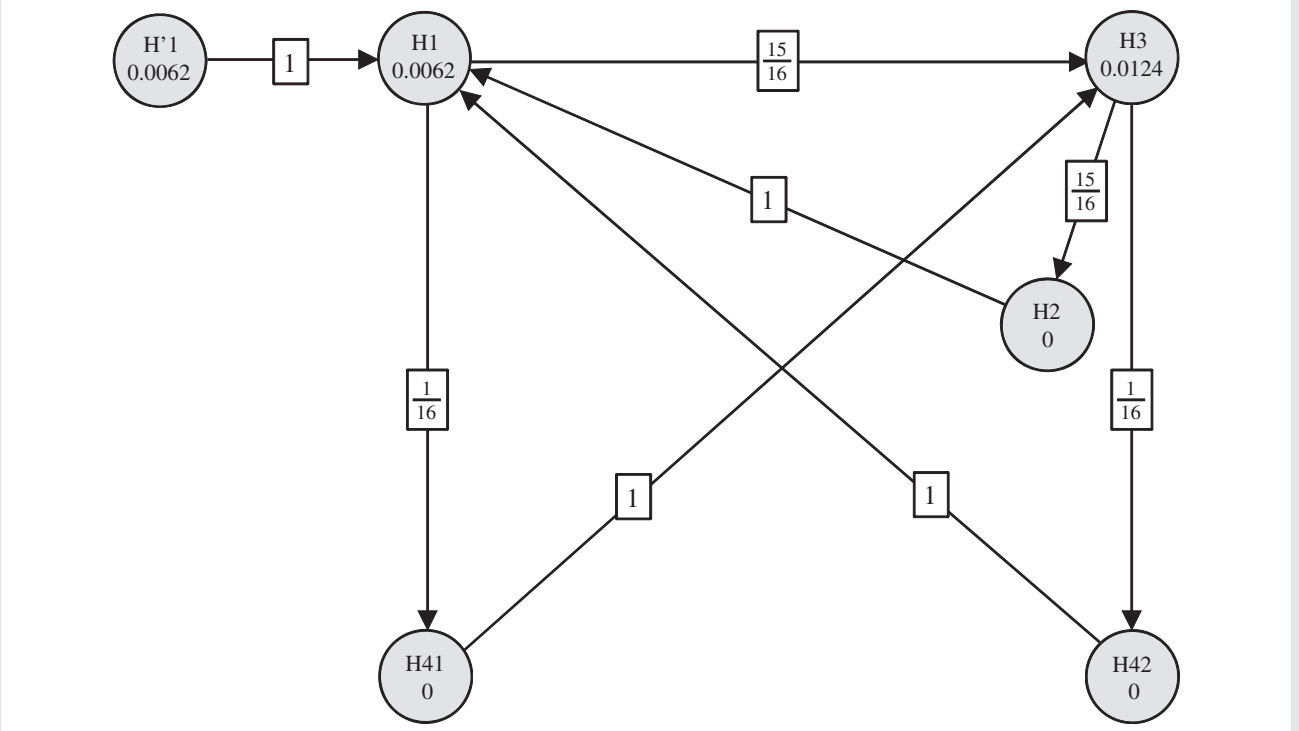

Figure 1 Graphical illustration and definition of the testing strategy. The primary null hypotheses are denoted by: H1 (superiority of combination enalapril plus aliskiren vs. enalapril alone in the entire study population); H′1 (superiority of combination vs. enalapril in patients without diabetes); H2 (superiority of aliskiren monotherapy vs. enalapril monotherapy); and H3 (non-inferiority of aliskiren monotherapy vs. enalapril). The key secondary hypotheses are designated H41 and H42 (superiority of combination therapy vs. enalapril and aliskiren monotherapy vs. enalapril for the Kansas City Cardiomyopathy Questionnaire clinical summary score). The initial allocation of significance levels are $\alpha/4$, $\alpha/4$, $\alpha/2$, 0, 0, 0 for H1, H′1, H3, H2, H41, and H42, respectively. If a hypothesis can be rejected, the relocation of its significance level to one of the other hypotheses is as shown in the Figure. The relocation of the significance level and the specified portion of the significance level (as a fraction) is shown by the arrows in the Figure. The sequentially rejective multiple test procedure is completed when no hypothesis can be rejected anymore. The significance levels are rounded to four decimals based on $\alpha = 0.025$. The final significance level presented will also be adjusted for interim analyses. To illustrate this further, if the initial test for H′1 at the 0.0062 significance level is attained, the entire 0.0062 significance level will be relocated (carried forward) to test H1. As a consequence, the test for H1 can be made at a significance level of 0.0124 (i.e. the relocated 0.0062 from H′1 plus the initial 0.0062 for H1). If the test for H′1 is not significant, the 0.0062 initially allocated to H′1 is completely spent, without any carry forward to test H1. As another example, if the test for H1 is statistically significant at any stage, 15/16 of the significance level available for H1 at that stage will be relocated to H3 and 1/16 carried forward to H41. The testing procedure will continue and be completed until no further hypothesis can be rejected.

relation to the use of aliskiren in addition to an ACE inhibitor or ARB in patients with diabetes, and given the additional primary analysis of trial outcomes in individuals without diabetes at baseline. In view of the specific concerns raised in relation to the use of aliskiren in addition to an ACE inhibitor or ARB in patients with diabetes, and the additional primary analysis of trial outcomes in individuals without diabetes at baseline, a breakdown of patient characteristics according to diabetes status at baseline is also reported. Diabetes status at the time of randomization was determined according to investigator designation at screening plus confirmed new cases of diabetes occurring during the run-in period.

Results

Patients were randomized into ATMOSPHERE between April 2009 and April 2014 at 755 sites in 43 countries. Key baseline variables are summarised in *Table 3*.

Baseline characteristics in ATMOSPHERE and comparison with PARADIGM-HF

The characteristics of patients in ATMOSPHERE and PARADIGM-HF were, for the most part, very similar: most were male, middle-aged, and Caucasian. A majority had a history of coronary heart disease and just over one-third had a history of atrial fibrillation. The NYHA class distribution and mean LVEF were similar, as was the mean Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score. There was a very high rate (>90%) of treatment with a beta-blocker in both trials.

There were, however, some notable differences. The proportion of patients with diabetes was lower in ATMOSPHERE than in PARADIGM-HF (28% vs. 35%), as was the proportion with a history of hypertension (62% vs. 71%), although, at randomization,

Table 2 Revised power scenarios for superiority

Risk reduction	Power (%) H_1* ($\alpha = 0.62375\%$ one-sided, not adjusted for safety interim looks)	Power (%) H_2 ($\alpha = 1.16719\%$ one-sided, not adjusted for safety interim looks)
15%	75%	82%
16.5%	85%	89%
18%	91%	94%

*For H_1 risk reductions of 15.7% or larger can be detected with a power of at least 80%. H_1 refers to the primary hypothesis comparing the superiority of the combination enalapril plus aliskiren vs. enalapril alone in the entire study population) and H_2 to the co-primary hypothesis comparing the superiority of aliskiren monotherapy vs. enalapril monotherapy. For H_3 (non-inferiority comparison of aliskiren with enalapril), the power will remain >80% provided there is a relative risk reduction for aliskiren compared with enalapril of at least 6%.

systolic blood pressure was higher in ATMOSPHERE than in PARADIGM-HF (124 mmHg vs. 121 mmHg), as was the proportion of Asian patients.

Mean estimated glomerular filtration rate (eGFR) at randomization was also higher in ATMOSPHERE at 74 mL/min.1.73 m^2, compared with 68 mL/min.1.73 m^2 in PARADIGM-HF. The proportion of patients with an eGFR <60 mL/min.1.73 m^2 was correspondingly smaller in ATMOSPHERE than in PARADIGM-HF (27% vs. 35%).

Median plasma NT proBNP concentration at randomization was slightly lower in ATMOSPHERE (1467 pg/mL) than in PARADIGM-HF (1615 pg/mL). Lastly, use of a MRA was much lower in ATMOSPHERE (37%) compared with PARADIGM-HF (56%).

The proportion of patients with an implantable cardioverter defibrillator was low overall in ATMOSPHERE (as in PARADIGM-HF) but this varied greatly by region with a device in 55% of ATMOSPHERE patients enrolled in North America, 34% in Western Europe but only 6.6% in the rest of the world.

Comparison of baseline characteristics in patients with and without diabetes in ATMOSPHERE

There were many differences between the characteristics of patients with and without diabetes in ATMOSPHERE (*Table 4*). Patients with diabetes were older and had generally worse overall HF status (as judged by NYHA class, KCCQ overall summary score, signs of heart failure, NT-proBNP concentration, regular diuretic use, and history of HF hospitalization). Mean LVEF in individuals with diabetes was the same as in those without diabetes (28%). Patients with diabetes had a higher body mass index and had more co-morbidity, especially a history of hypertension (74% vs. 57%) and coronary heart disease. Mean eGFR was slightly lower in those with diabetes and the proportion with an eGFR <60 mL/min.1.73 m^2 was slightly higher compared with individuals without diabetes. Other than diuretics, the use of HF medications (including MRAs) was similar in patients with and without diabetes,

Table 3 Baseline characteristics of patients in ATMOSPHERE compared with those in PARADIGM-HF

	ATMOSPHERE ($N = 7063$)	PARADIGM-HF ($N = 8399$)
Age at screening visit, years	63	64
Male sex, %	78	78
Race, %		
Caucasian	66	66
Black	2	5
Asian	25	18
Other	7	11
Cause of heart failure		
Ischaemic aetiology, %	56	60
NYHA functional class %		
Class I	2	5
Class II	69	71
Class III	28	24
Class IV	1	1
Signs of heart failure		
Rales, %	10	8
Third heart sound, %	8	9
JVP elevation, %	9	10
Peripheral oedema, %	21	21
KCCQ (points)		
KCCQ mean clinical summary score	75	73
Median NT-proBNP, at screening visit,‡ (IQR) pg/mL	1467 (850–2664)	1615 (888–3231)
Physiological measures		
LVEF at screening visit, %	28	29
Heart rate, bpm*	72	72
SBP, mmHg		
at screening visit,	127	128
at randomization visit,	124	121
Median BMI, kg/m^2	27	28
Laboratory measures		
Serum creatinine, μmol/L	92	99
Serum potassium, mmol/L	4.5	4.5
eGFR, mL/min.1.73 m^2	74	68
eGFR <60 mL/min.1.73 m^2, %	27	36
Medical history†		
Previous heart failure hospitalization, %	60	63
Hypertension, %	62	71
Stable angina pectoris, %	19	20
Unstable angina pectoris, %	11	12
Myocardial infarction, *n* (%)	41	43
Percutaneous coronary intervention, %	20	21
Coronary artery bypass graft, %	14	16
Atrial fibrillation based on history, %	34	37

Table 3 Continued

	ATMOSPHERE (*N* = 7063)	PARADIGM-HF (*N* = 8399)
Atrial fibrillation based on ECG	23	25
Diabetes mellitus, %	28	35
Stroke, %	7	9
Current smoker, %	13	14
ECG findings		
Left bundle branch block (%)	21	20
QRS duration, ms	117	117
Pre-trial use of ACE inhibitor/ARB		
Previous use of ACE inhibitor at screening visit, %	100	78
Previous use of ARB at screening visit, %	2	23
Pharmacological treatment		
Diuretic use, %	80	80
Beta-blocker, %	92	93
MRA, %	37	56
Digoxin, %	32	30
Anticoagulant, %	30	32
Aspirin, %	51	52
Any antiplatelet agent, %	55	56
Lipid lowering, %	52	56
Devices for HF at screening		
CRT, %	6	7
ICD, %	15	15

All values are from the randomization visit unless otherwise stated. For NT-proBNP values are shown as median and 25%/75% interquartile ranges. Percentages reported are those with available data. Value at randomization visit is the last non-missing value at or before the randomization visit. Percentages may not total 100 because of rounding.
ATMOSPHERE, aliskiren trial to minimize outcomes in patients with heart failure trial; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; JVP, jugular venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; PARADIGM-HF, prospective comparison of angiotensin receptor neprilysin inhibitors with angiotensin converting enzyme inhibitors to determine impact on global mortality and morbidity in heart failure trial; SBP, systolic blood pressure.
*Atrial fibrillation and diabetes mellitus are at randomization. All other medical history variables are from the screening visit except history of atrial fibrillation and diabetes mellitus.
†Measured as pulse rate.
‡NT pro BNP measurements were available in 5924 patients in ATMOSPHERE.

although treatments for coronary heart disease (anti-platelet and lipid-lowering therapy) were used more frequently in subjects with diabetes.

Discussion

The mandate by the CTFG to stop study treatment in patients with diabetes created a number of problems for ATMOSPHERE. These included the effort required of investigators to identify and

Table 4 Baseline characteristics of patients in ATMOSPHERE according to baseline diabetes status

	ATMOSPHERE Diabetes status	
	Yes (*n* = 1958)	No (*n* = 5105)
Age at screening, years	65	63
Male sex, %	78	78
Race, %		
Caucasian	68	65
Black	1	2
Asian	25	25
Other	6	7
Cause of heart failure		
Ischaemic aetiology, %	67	52
NYHA functional class, %		
Class I	2	3
Class II	67	70
Class III	30	27
Class IV	1	1
Signs of heart failure		
Rales, %	12	9
Third heart sound, %	8	8
JVP elevation, %	9	9
Peripheral oedema, %	26	19
KCCQ, points		
KCCQ mean clinical summary score	72	76
Median NT-proBNP (IQR) at screening,‡ pg/mL	1425 (796–2558)	1494 (878–2735)
Physiological measures		
LVEF at screening visit, %	29	28
Heart rate, bpm†	73	71
SBP, mmHg		
At screening visit,	129	126
At randomization visit,	126	123
Median BMI, kg/m^2	28	26
Laboratory measures		
Serum creatinine, μmol/L	93	92
Serum potassium, mmol/L	4.5	4.5
eGFR, mL/min.1.73 m^2	73	74
eGFR <60 mL/min/1.73 m^2, %	29	26
Medical history*		
Previous HF hospitalization, %	65	58
Hypertension, %	74	57
Stable angina pectoris, %	22	17
Unstable angina pectoris, %	14	10
Myocardial infarction, *n* (%)	48	38
Percutaneous coronary intervention (%)	24	18
Coronary artery bypass graft, %	20	12
Atrial fibrillation based on history, %	33	35
Atrial fibrillation based on ECG	22	24
Stroke, %	8	7

Table 4 Continued

	ATMOSPHERE Diabetes status	
	Yes ($n = 1958$)	No ($n = 5105$)
Current smoker, %	11	14
ECG findings		
Left bundle branch block, %	21	21
QRS duration, ms	116	117
Pre-trial use of ACE inhibitor/ARB		
Previous use of ACE inhibitor at screening visit, %	100	100
Previous use of ARB at screening visit, %	4	2
Pharmacological treatment		
Diuretic use, %	86	78
Beta-blocker, %	92	92
MRA, %	36	37
Digoxin, %	32	32
Anticoagulant, %	30	31
Aspirin, %	57	49
Any antiplatelet agent, %	62	53
Lipid lowering, %	63	48
Devices for HF at screening		
CRT, %	6.5	5.2
ICD, %	16	15

All values are from the randomization visit unless otherwise stated. Percentages reported are those with available data. Randomization visit is the last non-missing scheduled visit at or before visit 4. Percentages may not total 100 because of rounding. For NT-proBNP, values are shown as median and 25%/75% interquartile ranges

ATMOSPHERE, aliskiren trial to minimize outcomes in patients with heart failure trial; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; JVP, jugular venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRA, mineralocorticoid receptor antagonist; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; PARADIGM-HF, prospective comparison of angiotensin receptor neprilysin inhibitors with angiotensin converting enzyme inhibitors to determine impact on global mortality and morbidity in heart failure trial; SBP, systolic blood pressure.

*Atrial fibrillation and diabetes mellitus are at randomization. All other medical history variables are from the screening visit except history of atrial fibrillation and diabetes mellitus.

†Measured as pulse rate.

‡NT-proBNP measurements were available in 5924 patients in ATMOSPHERE.

contact relevant patients and arrange for return of study drug as well as prescription of alternative therapy. These investigators and patients also had to be persuaded as to the value of continuing follow-up after the study drug was discontinued. The exclusion of new patients with diabetes and the generally negative publicity surrounding aliskiren led to prolongation of the trial recruitment period. The protocol and statistical analysis plan had to be amended to censor the follow-up of patients with diabetes for the primary and other efficacy endpoints on the date of submission of the protocol amendment or earlier in accordance with country-specific regulatory requirements. As around 30% of patients recruited at the time of this amendment had diabetes, and because diabetes increases cardiovascular risk, loss of follow-up time in these individuals (and exclusion of new patients with diabetes) resulted in slower accrual of the target number of patients with a primary endpoint, i.e. only patients without diabetes could contribute to the pre-specified number of events after the protocol amendment and censoring. The combination of a prolonged recruitment period and longer than anticipated follow-up also resulted in 'investigator fatigue' which added to the earlier complexity of re-consenting patients after the findings of ALTITUDE and again after the results of ASTRONAUT. Despite these hurdles, ATMOSPHERE is nearing completion.

The patients enrolled in ATMOSPHERE are similar to those in the largest and most recent trial in HF-REF (i.e. PARADIGM-HF). This is not surprising as the two study protocols were very similar in design, although not identical (*Table 1*). These small differences in design and regulatory intervention in ATMOSPHERE led to some differences in the patients randomized in the two trials. The exclusion of new patients with diabetes part way through ATMOSPHERE reduced the overall proportion of patients with diabetes (28% in ATMOSPHERE vs. 35% in PARADIGM-HF) and this presumably mainly accounts for the difference in proportion of patients with a history of hypertension (62% vs. 71%), given the striking difference in prevalence of hypertension between patients with and without diabetes (74% vs. 57%). ATMOSPHERE also had a higher eGFR threshold for randomization ($\geq$35 compared with $\geq$30 mL/min.1.73 m^2 in PARADIGM-HF) explaining the higher average eGFR and smaller proportion of patients with an eGFR <60 mL/min.1.73 m^2 in ATMOSPHERE (27%) compared with PARADIGM-HF (36%). Median NT-proBNP concentration at randomization was slightly lower in ATMOSPHERE (1467 pg/mL) than in PARADIGM-HF (1615 pg/mL), an observation that is likely largely explained by the lower proportion of patients with diabetes and reduced eGFR in ATMOSPHERE compared with PARADIGM-HF. The systolic blood pressure at randomization was higher in ATMOSPHERE than in PARADIGM-HF (124 mmHg vs. 121 mmHg), despite the exclusion threshold in the latter trial being higher (patients excluded if systolic pressure <90 mmHg in ATMOSPHERE and <95 mmHg in PARADIGM-HF). This difference probably reflects the more powerful blood pressure lowering effect of combined angiotensin and neprilysin inhibition during the PARADIGM run-in period compared with the addition of aliskiren (at half the full dose) to an ACE inhibitor during the ATMOSPHERE run-in period. The other difference of note is in the proportion of patients prescribed a MRA (56% in PARADIGM-HF vs. 37% in ATMOSPHERE). This probably reflects the fact that the use of MRA was encouraged in the amended PARADIGM-HF protocol after the publication of the findings of Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) while the recruitment of PARADIGM-HF was ongoing. The ATMOSPHERE protocol did not specifically advocate the use of MRAs and, indeed, warned of the risk of hyperkalaemia if an MRA (or ARB) was added to study drug (which in one-third of patients was the combination of enalapril and aliskiren). Most of the recruitment into ATMOSPHERE had also occurred before the demonstration of the benefit of MRAs in HF-REF patients with mild symptoms, as shown in EMPHASIS-HF, and the corresponding

change in guidelines (the bulk of patients in PARADIGM-HF were recruited somewhat later than those in ATMOSPHERE).[12–14] Evaluation of efficacy and safety in patients taking an MRA will clearly be a key aspect of the analysis of the results of ATMOSPHERE, especially in patients randomized to dual treatment with enalapril plus aliskiren (i.e. those receiving 'triple therapy'). The large subset of patients in ATMOSPHERE treated with a MRA means that such analyses should have reasonable statistical power.

Overall, the patients in ATMOSPHERE are largely representative of contemporary ambulatory patients with chronic HF-REF and are well treated pharmacologically, compared with historical trials. However, patients with diabetes are somewhat under-represented (for the reasons described earlier) and MRA use is not as high as would probably now be the case following recent guideline updates.[13,14] Use of devices, particularly implanted cardioverter defibrillators, was low in ATMOSPHERE, but that was also the case in PARADIGM-HF and in the recent Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), probably reflecting the high proportion of patients enrolled outside the USA and Western Europe.[15] More than half of patients enrolled in North America and just over one third of those recruited in Western Europe had an implantable cardioverter defibrillator at baseline compared with less than 7% elsewhere in the world.

The differences between patients with and without diabetes in ATMOSPHERE were similar to those in previous studies which have consistently shown a worse overall HF status in patients with diabetes, despite, paradoxically, a similar or higher average LVEF.[16] Similarly, comorbidity was more common in patients with diabetes, although in ATMOSPHERE the higher prevalence of renal dysfunction in patients with diabetes may have been less pronounced than in previous studies because of the trial-specific lower eGFR exclusion criterion.

The regulatory concerns about the safety of aliskiren used in combination with an ACE inhibitor or ARB in patients with diabetes and the subgroup analysis of ASTRONAUT have also led us to amend the statistical analysis plan for ATMOSPHERE. While the effect of aliskiren in ASTRONAUT was neutral overall, the subgroup of patients with diabetes treated with aliskiren added to an ACE inhibitor or ARB did worse than those with added placebo; the converse was also observed (i.e. patients without diabetes appeared to do better with aliskiren). Indeed, among patients without diabetes there were nominally statistically significant reductions in the risk of the composite outcome of cardiovascular death or HF hospitalization (HR 0.80, 95% CI 0.61–0.94) and all-cause death (HR 0.69, 95% CI 0.50–0.94) at 12 months in those treated with aliskiren, compared with placebo. For this reason, we added a third primary superiority hypothesis (i.e. that combination enalapril/aliskiren therapy will be superior to enalapril monotherapy in patients without diabetes; *Figure 1*).

While we have randomized 1958 patients with diabetes, and although these patients are at higher risk of adverse clinical outcomes, follow-up for analysis of the effect of treatment will be truncated and we have three separate treatment groups. Consequently, we will not have sufficient power to make definitive statements about the efficacy and safety of aliskiren in patients with diabetes. However, this is a question of limited clinical interest at present given the current prohibition of use of aliskiren in combination with an ACE inhibitor or ARB in patients with diabetes.

We have not mentioned the potential results of ATMOSPHERE because at this stage any such discussion would be purely speculative and would need to cover a large number of possible outcomes. What is clear, however, is that the recent findings of PARADIGM-HF have 'raised the bar' with respect to the benefit of what any alternative treatment would need to exhibit to change practice.

In summary, the patients enrolled in ATMOSPHERE are similar to those in the largest and most recent trial in HF-REF (i.e. PARADIGM-HF) and, overall, they are largely representative of contemporary ambulatory patients with chronic HF-REF and are well treated pharmacologically, compared with historical trials.[11] ATMOSPHERE will determine whether patients with HF-REF (particularly those without diabetes) benefit clinically from the addition of a direct renin inhibitor to standard background therapy, including an ACE inhibitor and beta-blocker, and in many patients a MRA. ATMOSPHERE will also determine whether aliskiren alone is superior to, or at least non-inferior to, enalapril.

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